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A general method for synthesis of 2-heterocyclic *N*-methyliminodiacetic acid boronates

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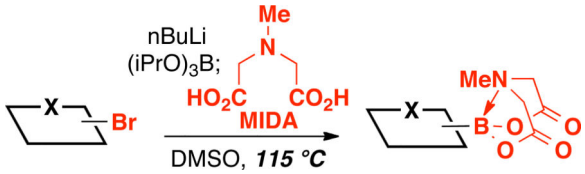
Abstract

A wide range of 2-pyridyl and other difficult-to-access heterocyclic *N*-methyliminodiacetic acid boronates can be readily prepared from the corresponding bromides via a new method involving direct transligation of trialkoxyborate salts with MIDA at elevated temperatures.

Graphical abstract



Most small molecules are highly modular in their constitution.[1,2] To maximally harness this inherent modularity, we aim to develop a general platform of building blocks representing the substructural motifs that most commonly appear in a wide range of targeted structures.[3] In this regard, a collection of air-stable and environmentally friendly 2-pyridyl building blocks represent a very important objective, as this subunit is found in many pharmaceuticals,[4] natural products and/or their derivatives,[5] unnatural nucleotides,[6] fluorescent probes,[7] metal-complexing ligands,[8] and materials.[9]

Although boronic acids are among the most desirable synthetic building blocks with respect to low cost, minimal environmental impact, and lack of toxicity, 2-pyridyl boronic acids are notoriously unstable, which precludes their effective utilization.[10] Many different types of surrogates for 2-heterocyclic boronic acids have been developed, including trifluoroborate salts,[11] trialkoxy or trihydroxyborate salts,[12] diethanolamine adducts,[13] sterically bulky boronic esters,[14] and boroxines.[15] Important advances with 2-heterocyclic silanolates have also recently been reported.[16] However, it remains a challenge to develop air-stable and chemically pure 2-pyridyl building blocks.[17]

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Supporting Information Available Procedures and characterization for all new compounds as well as spectral and X-ray crystallographic data.

We recently reported that 2-heterocyclic *N*-methyliminodiacetic acid (MIDA) boronates can serve as stable and highly effective surrogates for a wide range of unstable 2-heterocyclic boronic acids under "slowrelease" cross-coupling conditions.[3e] We also discovered that 2-pyridyl MIDA boronate **1a** is the first air-stable 2-pyridyl borane that can be isolated in chemically pure form and is a very convenient cross-coupling partner under modified slow-release conditions.[3e] However, our preliminary synthesis of this building block was cumbersome, low yielding, and not scalable.[3e] Given the broad potential utility of 2-heterocyclic MIDA boronates for many diverse applications,[4–9] we pursued a practical, scalable, and general method for their synthesis. Building on the surprising discovery that 2-pyridyl MIDA boronate **1a** is stable in anhydrous DMSO even at 130 °C, we herein report that a broad range of 2-pyridyl and other challenging-to-access heterocyclic MIDA boronates can be prepared from the corresponding readily-available bromides via a new method involving direct transligation of trialkoxyborate salts with MIDA at elevated temperatures (Fig. 1).

Lithium triisopropyl 2-pyridyl borate[18] **3** is known to be a useful intermediate for preparing other boronic acid surrogates[10,13] and for cross-coupling with a range of aryl halides.[12a] In preliminary studies, however, we were only able to achieve a low yield of **1a** from **3**.[3e] For example, the dropwise addition of a freshly prepared THF solution of **3** to a stirred suspension of MIDA in DMSO at 55 °C over 1 hour (Fig. 2A) resulted in a very low (~10%) and poorly reproducible yield of **1a** (Fig. 2B). A major byproduct observed in this reaction was pyridine, suggesting that protodeborylation of the notoriously labile 2-pyridyl–boron bond was a predominant competing pathway.

With the goal of minimizing this side reaction, we initially explored a wide range of complexation conditions involving milder temperatures. However, as shown in Fig. 2B, reducing the temperature always resulted in even lower yields of **1a**. Prompting us to reverse our approach, we discovered in parallel studies that **1a** is surprisingly stable in hot DMSO. For example, heating a solution of **1a** in d_6-DMSO at 130 °C for one hour caused no change in the ^{1}H NMR spectrum (see SI), which suggested that the undesired protodeborylation observed in the transligation reaction was occurring prior to MIDA complexation. This led us to question whether alternatively increasing the reaction temperature might enable a rapid transligation to form the very stable MIDA boronate **1a** prior to the decomposition of its precursor **3**. Consistent with this hypothesis, we discovered that raising the internal temperature from 55 to ≥ 115 °C resulted in a six-fold increase in the yield of **1a** (see Fig. 2B). Moreover, the procedure proved to be highly reproducible at these elevated temperatures.

This new method was easily reproduced on the gram scale to provide 2-pyridyl MIDA boronate **1a** in 59% isolated yield after silica gel chromatography (Table 1, entry 1). An optimized procedure was also developed for preparing **1a** on the decagram scale without the use of chromatography.[19] This highly crystalline building block has been stored as a solid on the benchtop under air without decomposition for more than 1 year (see SI for details).

A preliminary survey of scope has further revealed that a wide variety of 2-pyridyl bromides can also be transformed into the corresponding 2-pyridyl MIDA boronates using this same

methodology. Specifically, 6-, 5-, and 4-methyl-2-pyridyl subunits appear in a wide variety of pharmaceuticals, materials, and metal ligands, and the corresponding MIDA boronate building blocks **1b–1d** can be readily accessed on gram-scale (entries 2–4). It would also be highly advantageous in drug discovery to have access to a collection of air-stable 2-pyridyl building blocks having both electron-releasing and electron-withdrawing groups. Accordingly, 6-methoxy-, and 6-, 5-, and 4-trifluoromethyl-2-pyridyl MIDA boronates **1e–1h** were all prepared with this same procedure (entries 5–8). Bromo-substituted 2-pyridyl MIDA boronates **1i** and **1j**, each having the potential for a range of iterative cross-coupling applications,[3] were also conveniently synthesized via monofunctionalization of dibromo pyridines **2i** and **2j** (entries 9 and 10). Remarkably, all of these 2-pyridyl MIDA boronates **1a–j** are air- and chromatographically stable, highly crystalline, monomeric, free-flowing solids (SI).

Importantly, all of the reagents used in this novel protocol can be readily accessed for very low cost,[20] including the MIDA ligand. Using a new procedure involving reversed order of reagent additions compared to that reported previously,[3f,21] MIDA can now be easily prepared on the kilogram scale from the commodity chemicals iminodiacetic acid, formaldehyde, and formic acid (Scheme 1, see SI for details). Tens of thousands of metric tons of iminodiacetic acid are produced each year as a starting material for herbicides, surfactants, and environmental chelating reagents.[22] Thus, this starting material is very inexpensive.[23] Specifically, mol per mol, iminodiacetic acid is more than five times cheaper than *n*-BuLi.[20,23] MIDA is also completely biodegradable,[24] thus making MIDA boronates a very environmentally friendly alternative to the corresponding organostannanes.[17] Finally, the highly-crystalline and air-stable nature of MIDA boronates greatly facilitates their isolation, purification, and storage, making them highly attractive intermediates. Given all of these features, this new method stands to provide practical access to a wide range of 2-heterocyclic and other types of very useful MIDA boronate building blocks with an array of important applications. In fact, several of the new building blocks reported herein are already commercially-available.[25]

We have also preliminarily explored the potential of this new protocol to provide access to other types of very challenging-to-access heterocyclic boranes. For example, thiazole subunits appear in many pharmaceuticals, ligands, fluorescent probes, and materials, as well as a wide range of NRPS-derived natural products.[1,5c,26,27] However, the corresponding boronic acids again suffer from substantial stability issues.[26,27] Using an unoptimized version of this same protocol, 5-thiazolyl MIDA boronate **5** was accessed from the corresponding bromide **4**, and this new heterocyclic borane also proved to be indefinitely air-stable (SI, structure confirmed by X-ray, Scheme 2).

As a final example, 2-pyrazine subunits are very important in medicinal chemistry and many other applications.[28] However, to the best of our knowledge, there are no previously reported examples of air-stable 2-pyrazinyl borane building blocks. As shown in Scheme 3, using the standard conditions described above, 2-bromopyrazine **6** was effectively transformed into the corresponding 2-pyrazinyl MIDA boronate **7** (structure confirmed by X-ray), and this new building block has also proven to be indefinitely air-stable (SI).

In summary, we have developed a practical, scalable, and cost-effective method for preparing a wide range of previously challenging-to-access heterocyclic MIDA boronates involving direct transligation of the corresponding readily accessible triisopropoxyborate salts. Importantly, this new method completely avoids the intermediacy of boronic acids. In several cases, the building blocks described herein represent the first examples of the corresponding heterocyclic boranes that can be isolated as air-stable materials in chemically pure form. This methodology and the novel MIDA boronates that it can access stand to have a highly enabling impact on the synthesis of a wide range of pharmaceuticals, natural products, and materials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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19. (See SI for full details) To a stirred solution of 2-bromopyridine (9.5 mL, 97 mmol) and triisopropyl borate (19.5 mL, 84.8 mmol) in THF (175 mL) at −78 °C was added dropwise *n*-BuLi (2.5 M in hexanes, 36 mL, 90 mmol). The resulting solution was warmed to 23 °C and added over one hour to a stirred solution of MIDA (25.4 g, 173 mmol) in DMSO (175 mL) at 115 °C. The resulting mixture was cooled to 23 °C and filtered. The filtrate was deacidified with solid K_3PO_4 (72.6 g, 342 mmol) and concentrated in vacuo. The resulting residue was precipitated from CH_3CN:CH_2Cl_2:Et_2O to afford **1a** (11 g, 55%).
20. 2-Bromopyridine, *n*-BuLi, and $(i\text{-PrO})_3B$ can be purchased on the kg scale for <$20/mol (Spectrum Chemicals, Gardena, CA, USA), <$31/mol (Beta Pharma, New Haven, CT, USA) and < $28/mol (Matrix Scientific, Columbia, SC, USA), respectively.
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23. Iminodiacetic acid can be purchased on the kg scale for <$5.50/mol (City Chemical, West Haven, CT, USA).

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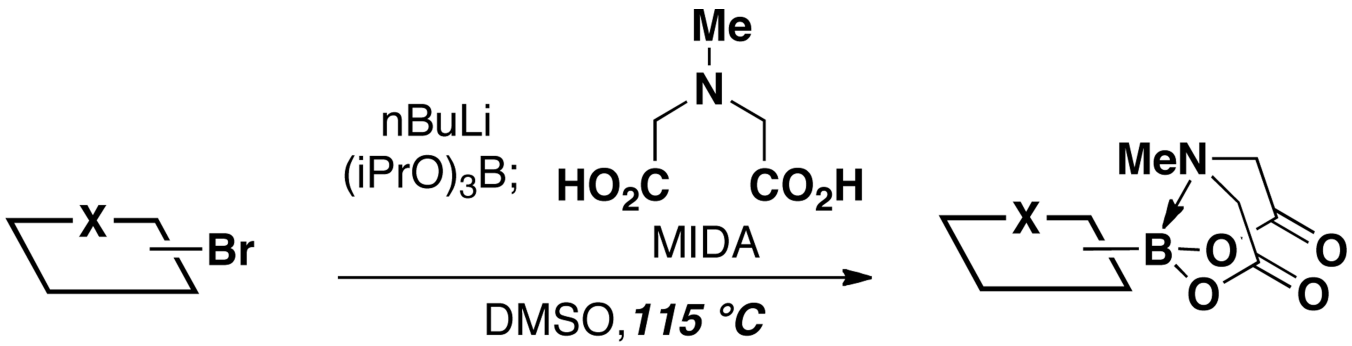


Figure 1.

A new method that provides access to a wide range of 2-pyridyl and other difficult-to-access MIDA boronates from the corresponding readily-available bromides.

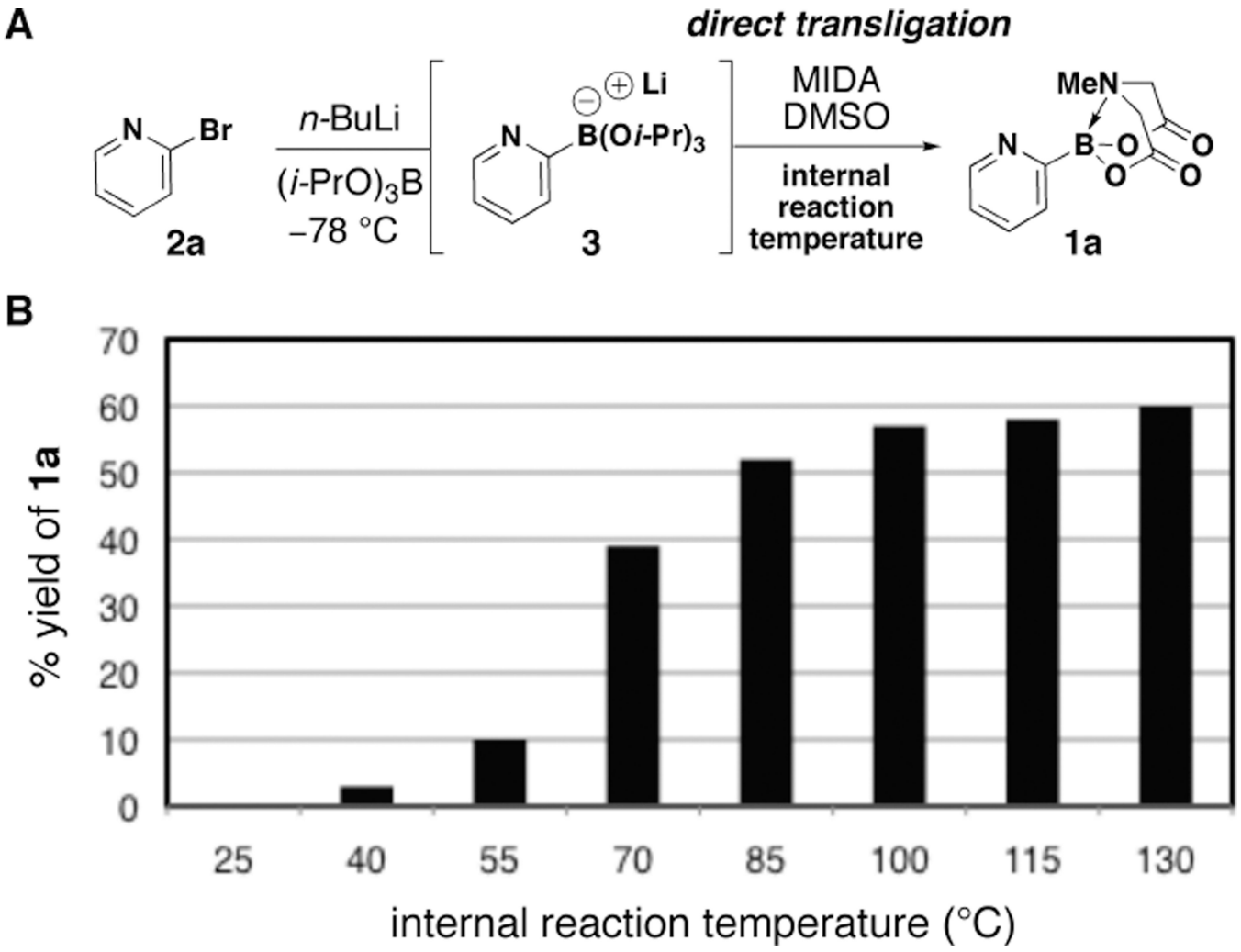
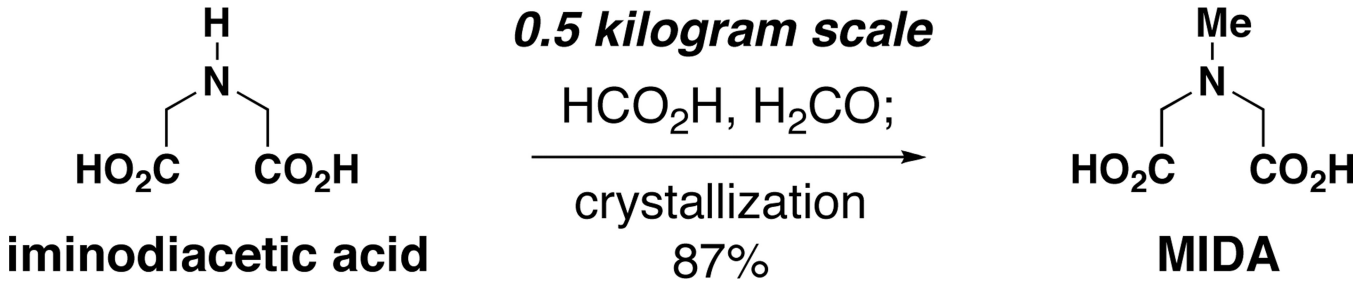
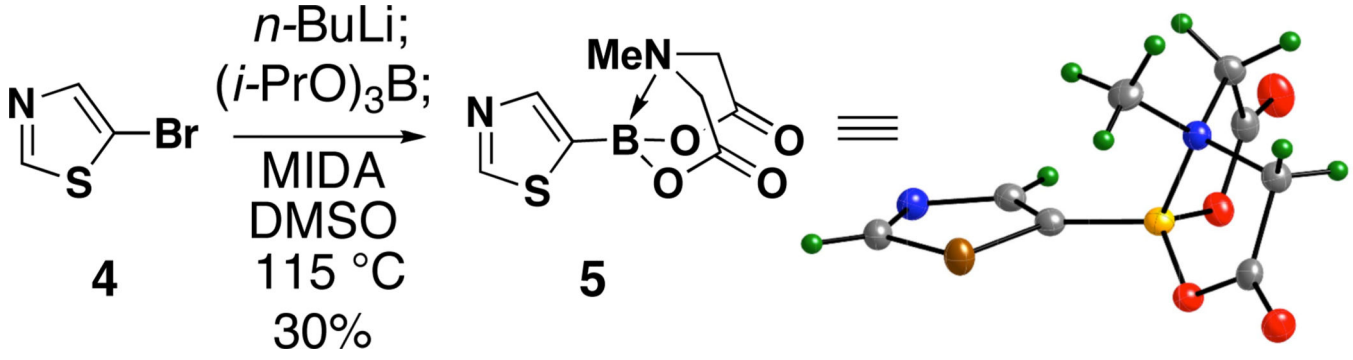


Figure 2.

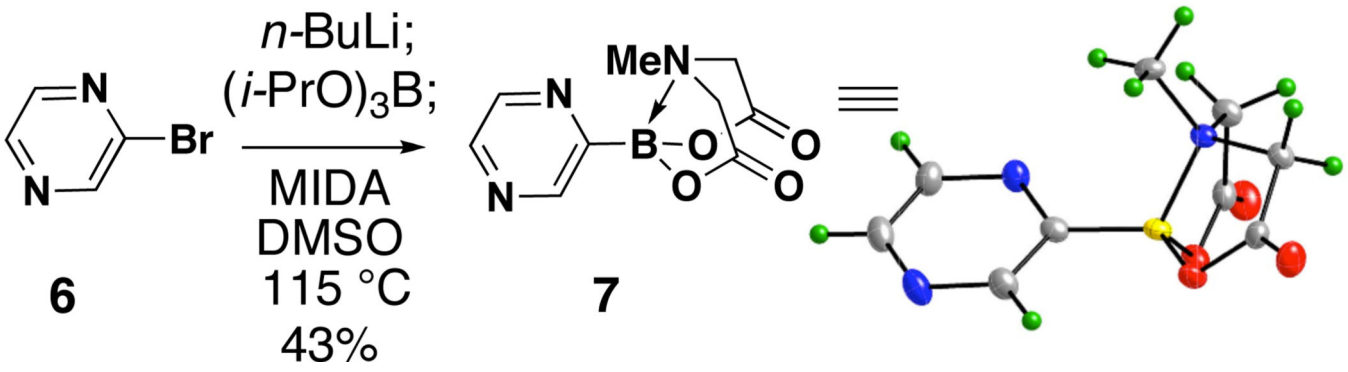
A. A method for the preparation of 2-pyridyl MIDA boronate **1a** from **2a** via the intermediacy of triisopropoxyborate salt **3**. **B.** Yield of **1a** (via ^{1}H NMR, average of two runs) as a function of the internal reaction temperature.



Scheme 1.



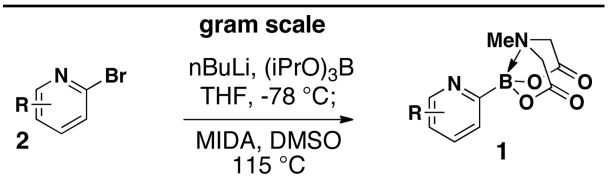
Scheme 2.



Scheme 3.

Table 1

Synthesis 2-pyridyl MIDA boronates.



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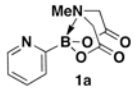
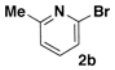
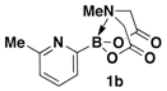
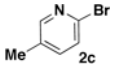
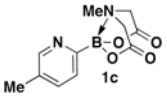
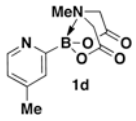
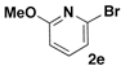
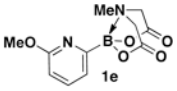
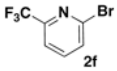
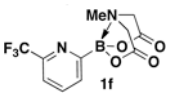
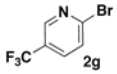
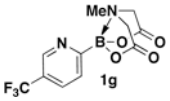
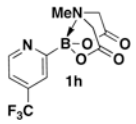
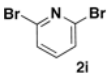
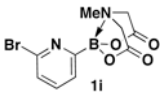
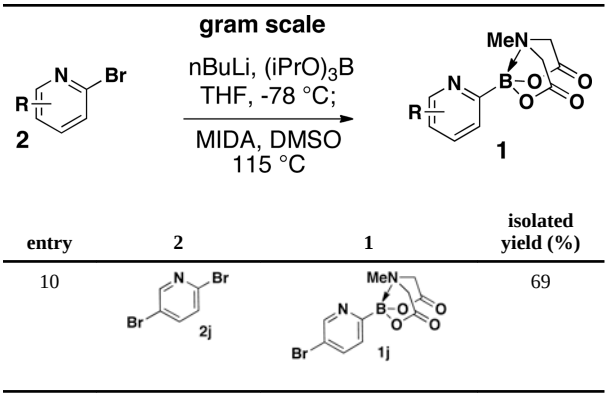
1			59
2			58
3			51
4			42
5			81
6			89
8			56
7			53
9			47



entry	2	1	isolated yield (%)
10	2j	1j	69